Development of Unit- Specific Anti- Pseudomonal Beta- Lactam Treatment Recommendations for Intensive Care Unit Patients Using Monte Carlo Simulation

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Abstract

Background: *Pseudomonas aeruginosa* (PsA) is the fifth leading pathogen isolated in nosocomial infections and associated with mortality rates as high as 50% in the setting of both bacteremia and ventilator associated- pneumonia. MCS is increasingly being utilized to predict the probability of target attainment (PTA) of antimicrobial dosing regimens by simulating drug exposures considering patient- derived pharmacokinetic parameters, agent specific pharmacodynamic targets, and organism susceptibility data. BL regimens optimized for enhanced PTA has been associated with improved clinical outcomes. We performed MCS to predict the PTA for various regimens of aztreonam (AZN), cefepime (CFP), meropenem (MPN), and piperacillin- tazobactam (PTZ) utilizing PsA susceptibility data from specific ICUs at our institution and pharmacokinetic data derived from the critically ill.

Methods: After receiving approval from our institutional review board, susceptibility data for non- urinary PsA isolates collected from patients admitted to the ICU between 2011 and 2012 were obtained and analyzed. Only first isolates from individual patients were included. Pharmacokinetic parameters including volume of distribution, clearance, and half- life for the included BLs were obtained from published studies in the critically ill population. Using Oracle Crystal Ball, 10,000 patient simulations were preformed to predict the PTA for both bolus and prolonged infusion (PI) regimens commonly employed in these patient care units. Upon completion of analysis, a simple single-page clinical decision tool for each ICU was constructed.

Results: 196 patient isolates were included. The PTA results for each anti- pseudomonal agent regimen in each ICU is displayed below.

Conclusions: These data show a significant variation in PTA for individual agents across different ICU locations. In addition, an approximately 25- 35% greater PTA was observed for CFP and MPN when compared to our institutions typical first- line agent, PTZ. These data are currently being employed to guide anti- pseudomonal agent selection and dosage in each of our ICU in an effort to maximize patient outcomes.

Background

- *Pseudomonas aeruginosa* (PsA) is the fifth leading pathogen isolated in nosocomial infections and associated with mortality rates as high as 50% in serious infections[1]
- Monte Carlo Simulation (MCS) is increasingly being utilized to predict the probability of antimicrobial regimens achieving identified pharmacodynamic targets using pharmacokinetic (PK) and microbiologic data[2, 3]
- *β*- lactam regimens guided by MCS have been associated with improved clinical outcomes[4]

Methods

Objective:
The objective of this study was to formulate unit- specific clinical decision tools for the selection of *β*- lactam regimens for the empiric treatment of PsA.

Study Design:
Monte Carlo Simulation

Setting and Population:
The project was conducted with Institutional Review Board approval at the University of Kentucky HealthCare (UKHC), a 540 bed tertiary care facility located in Lexington, Kentucky. All isolates were obtained from patients admitted to one of four ICU.

Microbiological Data:
AZN, CFP, MPN, and PTZ MICs for PsA isolated from ICU patients between 1/1/2011 and 12/31/2012 were included for analysis
MICs we re obtained using the BD Phoenix system
Only first isolates from individual patients were included
Urinary and cystic fibrosis isolates were excluded

Pharmacokinetic Data:
PK parameters were obtained from studies conducted in the critically ill with patients having CrCl approx. 80-120mL/min[5,6,7,8]
Volume of distribution (L) included were as follows:
AZN- 30.2 ±15, CFP- 21.8 ±5, MPN- 34.5 ±17, PTZ- 22.4 ±6
Half- life (h) included were as follows:
AZN- 2.3 ±0.9, CFP- 3 ±1.2, MPN- 2.2 ±1.2, PTZ- 1.2 ±0.6
Clearance (L/h) included were as follows:
AZN- 7.4 ±2.4, CFP- 8 ±2, MPN- 11.2 ±1.7, PTZ- 13.7 ±4.3

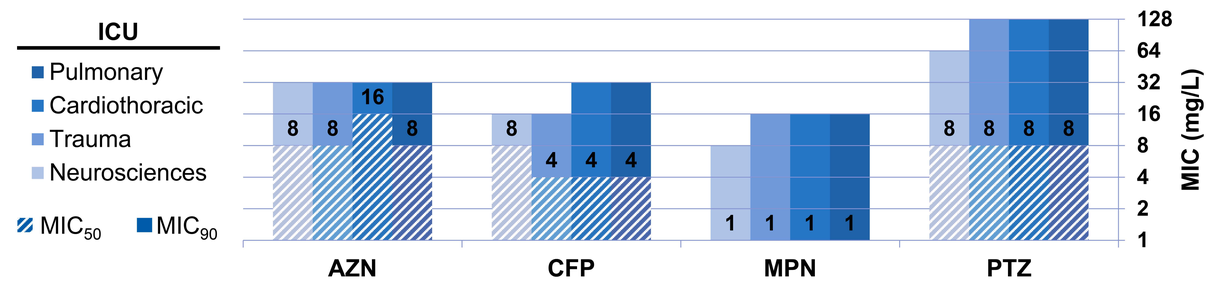
Pharmacodynamic Targets:
Target *f*T>MIC were obtained from the literature.
Target *f*T>MIC used were as follows:
AZN ≥50%, CFP ≥60%, MPN ≥40%, PTZ ≥50%

Monte Carlo Simulation:
10,000 simulations for each regimen in each ICU were preformed using Oracle Crystal Ball®

Construction of Clinical Decision Tool:
PTA for each regimen in each ICU were used to make a simple one page and color- coded clinical decision tool for each individual ICU.

Results

MIC_{50} and MIC_{90} Distributions by *β*- Lactam



Clinical Decision Tool Example– Trauma ICU

Aztreonam (AZN)	PTA
2g Q8 3hr Prolonged Infusion	52%
2g Q8	40%
1g Q8	19%
2g Q12	21%

Cefepime (CPM)	PTA
2g Q8 3hr Prolonged Infusion	90- 93%
2g Q8	86- 89%
1g Q8	74%
2g Q12	74%

Meropenem (MPN)	PTA
2g Q8 3hr Prolonged Infusion	85- 99%
2g Q8	85-93%
1g Q8	83%
2g Q12	84%

Piperacillin- tazobactam (PTZ)	PTA
4.5g Q6 3hr Prolonged Infusion	75%
4.5g Q6	58%
3.375g Q6	52%
4.5g Q8	44%

PTA Guide
≥90% - Excellent
75- 89% - Good
50- 74% - Poor
<50% - Very Poor

Conclusions

- The *β*- lactam MIC distribution for *Pseudomonas aeruginosa* was observed to be significantly varied among the different ICU
- The construction of a unit- specific clinical decision tool can highlight the importance of agent and dose selection to maximize the probability of target attainment in the treatment of infections such as those caused by PsA
- Further research is needed to continue to enhance the selection of antimicrobial therapy using local susceptibility data and population specific pharmacokinetic data.

References

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Disclosure:

The authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities.